INNOVATIONS IN TREATMENT OF PERIANAL CROHN DISEASE combined therapy

Cristina Marmorale
PERIANAL CROHN DISEASE

54% perianal complications in Crohn disease

22-23% occurrence of perianal Crohn disease

12% AT 1 YEAR
15% AT 5 YEARS
21% AT 10 YEARS
26% AT 20 YEARS

12% WITH ISOLATED ILEAL DISEASE
15% WITH ILEOCOLONIC DISEASE
41% WITH COLONIC DISEASE AND RECTAL SPARING
92% WITH COLONIC DISEASE INVOLVING THE RECTUM

LOW QUALITY OF LIFE

CLASSIFICATION OF PERIANAL LESIONS

**PRIMITIVE**
- FISSURES
- SKIN TAGS
- HEMORROID DISEASE
- PENTRATING ULCERS

**SECONDARY**
- FISTULAS
- ABSCESSES
- STENOSIS
- CANCER
PATHOGENESIS OF FISTULAE

ANAL GLAND INFECTION TRACKS ALONG INTERSPHINCTERIC SPACE

PENTRATING ULCERS (primary lesions) EXTEND WITH FORMATION OF ABSCESSES AND FISTULAS (secondary lesions)
ECCO Statement 9E
There is no consensus for classifying perianal fistulae in CD. In clinical practice most experts use a classification of simple or complex. From the surgical point of view Parks’ classification is more descriptive and can influence surgical decisions, but it is complicated to use in routine practice [EL5, RG D].

PARK’S Classification

(1) SUPERFICIAL
(2) INTER-SPHINCTERIC
(3) TRANS-SPHINCTERIC
(4) SUPRA-SPHINCTERIC
(5) EXTRA-SPHINCTERIC FISTULAS

AGA 2003 CLASSIFICATION

- PHYSICAL INSPECTION OF PERIANAL AREAS
- RECTOSIGMOIDOSCOPY

SIMPLE

COMPLEX

THIS CLASSIFICATION IS THE MORE USED IN CLINICAL PRACTICE. SIMPLE FISTULAS ARE MORE RESPONSIVE TO TREATMENT, INSTEAD COMPLEX FISTULAS ARE OFTEN REFERRATORY AND SURGERY CAN CAUSE INCONTINENCE IN SOME CASES

Gastroenterology 2003; 125:1508-1530
The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations


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DIAGNOSIS AND EVALUATION OF PERIANAL CROHN DISEASE
LOCATE THE ORIGIN OF THE FISTULA AND ITS ANATOMY

EVALUATE THE ORIGINATING INTESTINAL LOOP (INFLAMMATION OR STENOSIS)

DETERMINE WHICH ORGANS ARE AFFECTED AND THEIR CONTRIBUTION TO SYSTEMIC SYMPTOMS OR IMPAIRMENT OF THE QUALITY OF LIFE

IDENTIFY OR EXCLUDE LOCAL SEPSIS (ABSCESS)

ASSESS THE NUTRITIONAL STATUS OF THE PATIENT
ECCO Statement 9A
Pelvic MRI should be the initial procedure because it is accurate and non-invasive, although it is not needed routinely in simple fistulae [EL2b, RG B].
ECCO Statement 9B
Examination under anaesthetic is considered the gold standard only in the hands of an experienced surgeon. It may allow concomitant surgery, but care should be taken to obtain appropriate informed consent of the patient, since unexpected findings may preclude this [EL5, RG D].
ECCO Statement 9C
Anorectal ultrasound requires expertise, but can be equivalent to pelvic MRI in completing examination under anaesthesia if rectal stenosis has been excluded. [EL2b, RG B]. Fistulography is not recommended [EL3, RG C].
ECCO Statement 9D
Since the presence of concomitant rectosigmoid inflammation has prognostic and therapeutic relevance, proctosigmoidoscopy should be used routinely in the initial evaluation [EL2b, RG B].
CONVENTIONAL TREATMENT APPROACH FOR CROHN DISEASE

- Surgery
- Infliximab or adalimumab
- AZA/6-MP, MTX
- Prednisone, Budesonide
- 5-ASA, Antibiotics
# SURGICAL PROCEDURES FOR PERIANAL CROHN'S DISEASE

<table>
<thead>
<tr>
<th>Category</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emergency Treatment of Sepsis</strong></td>
<td>Incision and Drainage of Abscess</td>
</tr>
<tr>
<td><strong>Damage Limitation</strong></td>
<td>Seton Drain “Bridging” “Defunctioning Stoma”</td>
</tr>
<tr>
<td><strong>Definitive Treatment</strong></td>
<td>Fistulotomy Fistulectomy Flap Repair of Fistula Internal Sphincterotomy</td>
</tr>
<tr>
<td><strong>Intestinal Resection</strong></td>
<td>Proctectomy or Proctocolectomy Proximal Resection</td>
</tr>
</tbody>
</table>

*British journal of surgery 2004; 91: 801–814*
The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations


Received 19 August 2009; received in revised form 28 September 2009; accepted 28 September 2009
TREATMENT OF FISTULATING DISEASE

SIMPLE PERIANAL FISTULAE

1. Guideline: Asymptomatic Crohn’s fistulas need not be treated. Level of Evidence: IV; Grade: B. Asymptomatic Crohn’s fistulas may remain dormant and require no intervention. These patients, therefore, need not be subjected to the morbidity of operative intervention.49,51–53

2. Guideline: Simple, low Crohn’s fistulas may be treated by fistulotomy. Level of Evidence: IV; Grade: B. Healing rates after fistulotomy or intersphincteric and low transssphincteric Crohn’s fistulas range from 62 to 100% with reported minor incontinence rates of 0 to 12%.46,49–52,54–57 These wounds may take up to three to six months to heal.48

ECCO Statement 9G
For simple perianal fistulae it is important to know if they are symptomatic. If they are not, nothing has to be done. Only when simple fistulae are symptomatic are the options of non-cutting Seton or fistulotomy recommended [EL3, RG D]. Antibiotics, metronidazole (750–1500 mg/day) or ciprofloxacin (1000 mg/day), should be added [EL3, RG D].
EMERGENCY TREATMENT OF SEPSIS

ECCO Statement 9F
The presence of a perianal abscess should be ruled out and if present should be drained as a matter of urgency [EL5, RGD].

INCISION AND DRAINAGE OF ABSCESES

INSERTION OF SETON DRAIN

Surgical Approach to Perianal Abscess Drainage

Placement of drainage catheter

Placement of seton (suture)

A.

B.
“BRIDGING PERIOD”

Non cutting SETON

OOSTOMY

The Management of Perianal Crohn’s Disease Am J Gastroenterol 2007;102:S85-S87
Antibiotics and azathioprine/mercaptopurine should be used as the first choice of therapy for complex perianal Crohn's disease in combination with surgical therapy, in spite of a lack of clinical trials [EL4, RG D].

ECCO Statement 9K
3. Guideline: Complex Crohn’s fistulas may be well palliated with long-term draining setons. Level of Evidence: IV; Grade: B. The goal of a long-term loose (draining) seton for Crohn’s fistulas is to reduce the number of subsequent septic events by providing continuous drainage and preventing closure of the external skin opening. This goal can be achieved in 48 to 100% of such patients. Recurrent sepsis is seen approximately one-third of the time.\textsuperscript{41,46,51,53,58}

ECCO Statement 9H
Seton placement should be recommended [EL4, RGD] for complex fistulae. The timing of removal depends on subsequent therapy.

ECCO Statement 9I
Active luminal Crohn’s disease should be treated if present, in conjunction with appropriate surgical management of fistulae [EL5, RGD].
Antibiotics and azathioprine/mercaptopurine should be used as the first choice of therapy for complex perianal Crohn's disease in combination with surgical therapy, in spite of a lack of clinical trials [EL4, RG D].

ECCO Statement 9K

Infliximab [EL1b, RGA] or adalimumab [EL1b, RGB] should be used as a second line medical treatment [EL1b, RGB].
TREATMENT OF FISTULATING DISEASE

ONLY MEDICAL THERAPY?

May 6, 1999  The New England Journal of Medicine

INFLIXIMAB FOR THE TREATMENT OF FISTULAS IN PATIENTS WITH CROHN’S DISEASE


<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=31)</th>
<th>Infliximab 5/10 mg A 0-2-6 wk vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7 (23)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Abscess</td>
<td>1 (3)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (6)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

Complete closure in 46%
“A relevant clinical problem in treating perianal fistulas is the risk of abscess formation during infliximab therapy which affected about 10% of patients in the largest studies. The healing of the skin before closure of the fistula tract, shown using MRI and anal endosonography could favour abscess formation and fistula recurrence. **Setons, which aid fistula drainage, could reduce the risk of abscess and in permitting more complete fistula healing also the risk of recurrence**”
1° Antibiotics

2° Azathioprine, Mercaptopurine

3° Infliximab, Adalimumab

Surgery
Hippocrates, great Greek physician of the fifth century B.C., is pictured palpating a young patient. Kindliness and concern, embodied in his aphorism, "Where there is love for mankind, there is the love for the art of healing," are reflected in Hippocrates’ face. This revered practitioner, scientist, and teacher, well deserved the title, "Father of medicine," which has been associated with his name for more than 2,000 years.
**Combined Therapy**

**Treatment of perianal fistulizing Crohn's disease with infliximab alone or as an adjunct to exam under anesthesia with seton placement.**

Regueiro M, Mardini H.
University of Pittsburgh School of Medicine, Presbyterian Hospital, Pittsburgh, Pennsylvania 15261, USA.

**Combined seton placement, infliximab infusion, and maintenance munosuppressives improve healing rate in fistulizing anorectal Crohn’s disease: a single center experience.**

Topstad DR, Panaccione R, Heine JA, Johnson DR, MacLean AR, Buie WD.
Department of Surgery, Foothills Hospital, University of Calgary, Calgary, Alberta, C

**Infliximab in the surgical management of complex fistulating anal Crohn’s disease**

C. Talbot*, P. M. Sagar*, M. J. Johnston*, P. J. Finan* and D. Burke**
Division of Colon and Rectal Surgery, The General Infirmary at Leeds, United Kingdom

**Fistulating Anal Crohn’s Disease: Results of Combined Surgical and Infliximab Treatment**


**Combined therapy with infliximab and seton drainage for perianal fistulizing Crohn’s disease with anal endosonographic monitoring: a single-centre experience**

Dipartimento di Scienze Chirurgiche Università Cattolica del Sacro Cuore, Roma, Italy

**Predicting Factors of Fistula Healing and Clinical Remission After Infliximab-Based Combined Therapy for Perianal Fistulizing Crohn’s Disease**

David Tougeron, Guillaume Savoye, Céline Savoye-Collet, Edith Koning, Francis Michot, Eric Lerebours
Department of Surgery, Rouen University Hospital C Nicolle, 1 rue de Germont, 76031 Rouen, France
Treatment of complex perianal fistulas in Crohn disease: infliximab, surgery or combined approach

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From the Divisions of *General Surgery and Gastroenterology, Second University of Naples, Naples, and the †Division of Digestive Endoscopy, Clinica Pineta Grande, Castel Volturno (Caserta), Italy

Table 2. Outcome of interventions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Infliximab (group A), n = 11</th>
<th>Surgery (group B), n = 10</th>
<th>Infliximab + surgery (group C), n = 14</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment response, no. of patients*</td>
<td></td>
<td></td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.74</td>
</tr>
<tr>
<td>Partial response</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Complete response</td>
<td>7</td>
<td>7</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td>Proctectomy or diversion</td>
<td>1/11</td>
<td>2/10</td>
<td>0/14</td>
<td>0.2</td>
</tr>
<tr>
<td>Healed†</td>
<td>4/7</td>
<td>4/7</td>
<td>9/11</td>
<td>0.9</td>
</tr>
<tr>
<td>Healing time of fistula,† mean (SD), mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0 (0.8)</td>
<td>4.2 (1.3)</td>
<td>3.1 (0.8)‡</td>
<td></td>
</tr>
<tr>
<td>Recurrent fistula</td>
<td>3/7</td>
<td>3/7</td>
<td>2/11</td>
<td>0.2</td>
</tr>
<tr>
<td>Time to relapse, mean (SD), mo</td>
<td>2.6 (0.7)§</td>
<td>3.6 (0.5)§</td>
<td>10.1 (2.4)§</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation.
*Patients assessed at 6-month follow-up visit.
†Refers to patients with a complete response.
‡p < 0.05 v. group B.
§p < 0.05 v. group C.
Predicting Factors of Fistula Healing and Clinical Remission After Infliximab-Based Combined Therapy for Perianal Fistulizing Crohn’s Disease

David Tougeron · Guillaume Savoye · Céline Savoye-Collet · Edith Koning · Francis Michot · Eric Lerebours

<table>
<thead>
<tr>
<th></th>
<th>Responder patients $n = 13$</th>
<th>No responder patients $n = 13$</th>
<th>$P$ (univariate)</th>
<th>$P$ (multivariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>35.1 ± 15.0</td>
<td>38.6 ± 9.8</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>CD duration (year)</td>
<td>9.9 ± 8.6</td>
<td>8.6 ± 8.1</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Smoking status ($n$, %)</td>
<td>2 (15.4%)</td>
<td>4 (30.8%)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Previous intestinal resection ($n$, %)</td>
<td>4 (30.8%)</td>
<td>7 (53.8%)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Albumin rate</td>
<td>27.4 ± 2.5</td>
<td>30.9 ± 3.7</td>
<td>$P = 0.03$</td>
<td>$P = 0.08$</td>
</tr>
<tr>
<td>CRP</td>
<td>48.1 ± 25.3</td>
<td>33.8 ± 26.0</td>
<td>$P = 0.18$</td>
<td></td>
</tr>
<tr>
<td>CD-related hospitalizations</td>
<td>0.7 ± 0.7</td>
<td>1.1 ± 1.4</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td><strong>CDAI at first infliximab infusion</strong></td>
<td>142 ± 78</td>
<td>218 ± 102</td>
<td>$P = 0.04$</td>
<td>$P = 0.41$</td>
</tr>
<tr>
<td>Immunosuppressant at inclusion</td>
<td>12 (92.3%)</td>
<td>9 (69.2%)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Associated luminal disease ($n$, %)</td>
<td>1 (7.7%)</td>
<td>7 (53.8%)</td>
<td>$P = 0.03$</td>
<td>$P = 0.19$</td>
</tr>
<tr>
<td><strong>PCD characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ano-vaginal fistula ($n$, %)</td>
<td>4 (30.8%)</td>
<td>4 (30.8%)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Complex PCD ($n$, %)</td>
<td>8 (61.5%)</td>
<td>10 (76.9%)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Inter or extraspincteric track ($n$, %)</td>
<td>8 (61.5%)</td>
<td>7 (53.8%)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Abscess ($n$, %)</td>
<td>5 (38.5%)</td>
<td>6 (46.1%)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Associated rectal involvement ($n$, %)</td>
<td>3 (23.1%)</td>
<td>10 (76.9%)</td>
<td>$P = 0.01$</td>
<td>$P = 0.047$</td>
</tr>
<tr>
<td><strong>Initial IRM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperintensity (average ± ET)</td>
<td>8</td>
<td>7.7 ± 1.1</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>MRI score (average ± ET)</td>
<td>13.7 ± 4.3</td>
<td>13.1 ± 4.6</td>
<td>ns</td>
<td></td>
</tr>
</tbody>
</table>
Local Injection of Infliximab for the Treatment of Perianal Crohn’s Disease

G. Poggioli, M.D.,¹ S. Laureti, M.D.,¹ F. Pierangeli, M.D.,¹ F. Rizzello, M.D.,² F. Ugolini, M.D.,¹ P. Gionchetti, M.D.,² M. Campieri, M.D.²

pilot study

Treatment Of Perianal Fistulas In Crohn's Disease By Local Injection Of Antibody To Tnf-alpha Accounts For A Favourable Clinical Response In Selected Cases: A Pilot Study.

Asteria Cr , Ficari F , Bagnoli S , Milla M , Tonelli F.
LOCAL THERAPY: WILL BE THE FUTURE?

TOPICAL TACROLIMUS
FIBRIN GLUE
INTRALESION INFlixIMAB
ADIPOSE DERIVED STEM CELL TERENCE
FISTULA PLUG